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COMPLETE SPECIFICATION

Cyclopentanophenanthrene Derivatives and process for the Production thereof

We, SYNTEX S.A., Apartado Postal 2679, Mexico City, Mexico, a Corporation of Mexico, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

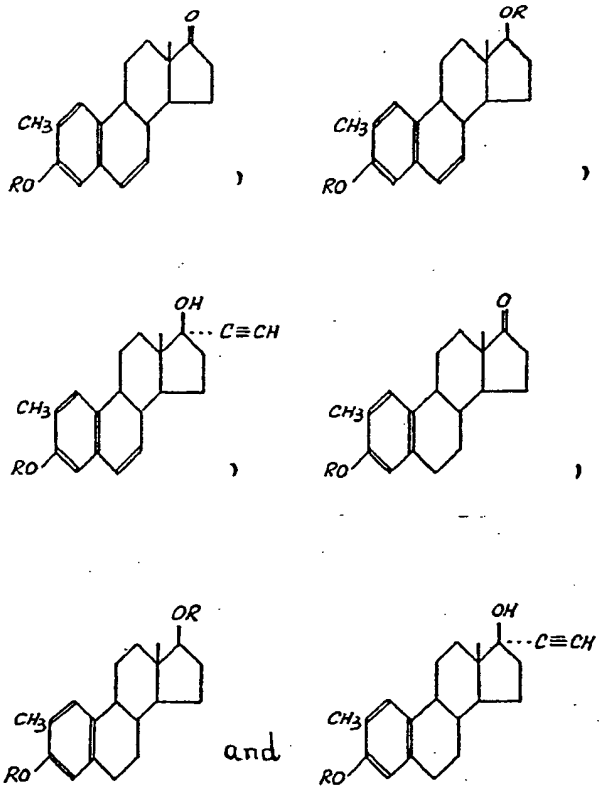
The present invention relates to cyclopentanophenanthrene compounds and to a process for the production thereof.

The present invention relates especially to novel 2-methyl estrone and estradiol derivatives and to a novel process for the production thereof. The novel compounds of the present invention are estrogenic hormones generally suitable for the treatment of prostate cancer, i.e., they show lesser estrogenic activity together with valuable anti-androgenic activity.

In our application 16962/57 (Serial No. 857,080) there is disclosed the production of 2 - methyl - $\Delta^{1,4,6}$ - androstatriene - 3,17 - dione. In accordance with the present invention it has been discovered that this compound when subjected to pyrolysis at approximately 600° C. aromatizes to form 2-methyl-6-dehydro-estrone, an estrogenic hormone and intermediate for the production of other novel 2-methyl-estrone and estradiol derivatives. These are 2 - methyl - 6 - dehydro-estradiol, 2 - methyl - 17α - ethinyl - 6 - dehydro-estradiol, 2 - methyl - estrone, 2 - methyl-estradiol, and 2 - methyl - 17α - ethinyl-estradiol compounds. From these compounds by conventional means there may also be prepared their novel esters of hydrocarbon carboxylic acids of less than 12 carbon atoms.

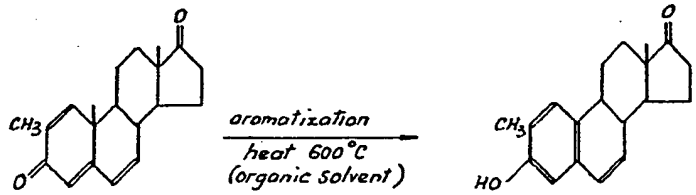
The novel 2-methyl estrone and estradiol derivatives of the present invention may therefore be represented by the following formulae.

[*Price 3s. 6d.*]



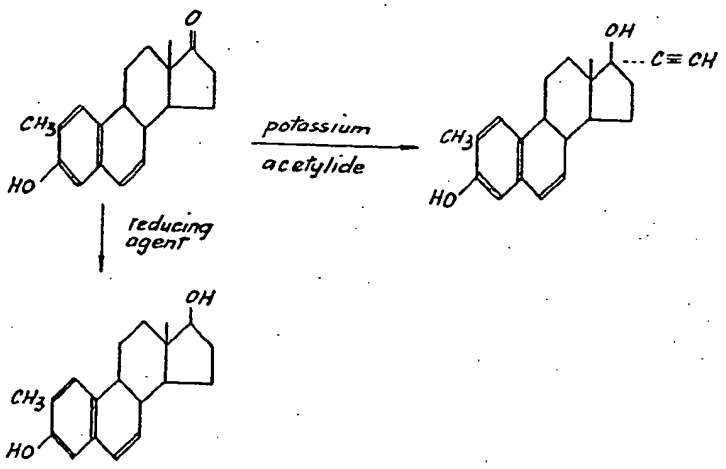
In the above formulae R represents an acyl group derived from a hydrocarbon carboxylic acid of less than 12 carbon atoms such as acetic, propionic, caproic, benzoic, cyclopentylpropionic or phenylpropionic, or R represents hydrogen.

A part of the process of the present invention may be exemplified by the following equation:



In practising one form of process above outlined the reaction is preferably performed by passing a dilute solution, as for example 1—2% by weight, of the 2 - methyl - $\Delta^{1,4,6}$ - androstatriene-3,17-dione, through a tube or column filled with glass helices and heated to a temperature as for example of 600° C. and preferably between 500° and 650° C. The solvents used are preferably hydrogen donor solvents such as tetrahydronaphthalene, mineral oil, dihydronaphthalene, dihydrophenanthrene and cyclohexene. After passage through the tube the hot reaction solution is diluted with an organic solvent such as hexane and the product (2 - methyl - 6 - dehydroestrone) purified, e.g., by chromatographic treatment and crystallization. From the free compound by conventional acylation procedures such as reaction with the corresponding acid anhydrides or acyl halides there are then prepared esters of hydrocarbon carboxylic acids of less than 12 carbon atoms such as those previously set forth.

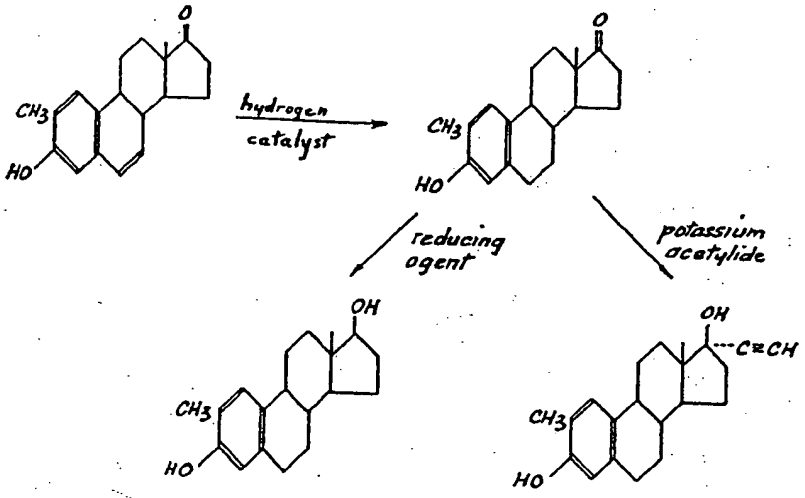
The 2 - methyl - 6 - dehydro - estrone is utilized for the preparation of 2-methyl-6-dehydro-estradiol and 2-methyl-17α-ethinyl-6-dehydro-estradiol in accordance with the following scheme:



To prepare the ethinyl derivative as indicated above the 17-keto compound may be reacted with potassium acetylide prepared *in situ*. Thus the 2-methyl-6-dehydro-estrone may be dissolved in an organic solvent, such as benzene, and added to a solution of potassium metal in a tertiary alcohol such as *t*-butyl alcohol. Acetylene is then passed into the reaction mixture for a prolonged period of time of the order of 2 days. Neutralization with acid and removal of the organic solvents by steam distillation results in a precipitate of the 17α-ethinyl product which is purified, e.g., by crystallization.

For the production of the estradiol derivative the estrone compound is treated with a reducing agent, preferably an alkali metal hydride such as sodium borohydride or lithium aluminium hydride in alcohol-water solution.

Similarly with prior hydrogenation the 2-methyl-6-dehydroestrone can be utilized for the preparation of 2-methyl-estrone, 2-methyl-estradiol and 2-methyl-17α-ethinyl-estradiol in accordance with the following scheme:



As indicated above hydrogenation in the presence of a hydrogenation catalyst, preferably palladium or platinum, until 1 mol of hydrogen is taken up gives the corresponding 2-methyl-estrone. Reaction with a reducing agent or with potassium acetylide as previously described in connection with the 6-dehydro compounds gives the corresponding 2-methyl estradiol and 17α-ethinyl-estradiol derivatives.

It may be noted further that all of the non-tertiary alcohol groups in both the 6-dehydro and corresponding 6-saturated compounds previously described may be conventionally esterified as with acid anhydrides or acyl halides to give either mono or diesters as previously indicated.

The following specific examples serve to illustrate but are not intended to limit the present invention.

EXAMPLE I

A solution of 2.0 g. of 2 - methyl - $\Delta^{1,4,6}$ - androstatriene-3,17-dione in 200 cc. of mineral oil was passed through a column packed with glass helices previously heated to 600° C., and this temperature was maintained during the operation. The solution was diluted with hexane and passed through a chromatographic column with 300 g. of alumina. The column was well washed with hexane to completely remove the mineral oil and then it was eluted with ether. The crystalline fractions were combined and crystallized from methanol to give 2-methyl-6-dehydro-estrone.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3-propionate, 3-benzoate, 3-cyclopentylpropionate and the 3-phenylpropionate.

EXAMPLE II

0.3 g. of 2-methyl-6-dehydro-estrone, dissolved in 20 cc. of methanol, was treated with a solution of 0.2 g. of sodium borohydride in 3 cc. of water and kept for 3 hours at room temperature. A few drops of acetic acid were then added and the solution was diluted with salt water. The precipitate was collected, washed with water and crystallized from acetone-hexane, thus giving 2 - methyl-6-dehydro-estradiol.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3,17-dipropionate, 3,17-dibenzoate, 3,17-dicyclopentylpropionate and the 3,17-diphenylpropionate.

EXAMPLE III

A solution of 0.5 g. of 2-methyl-6-dehydro-estrone in 20 cc. of anhydrous benzene was added under an atmosphere of nitrogen to a cooled solution of 0.5 g. of potassium metal in 25 cc. of *t*-butyl alcohol, which had also been prepared under a stream of nitrogen. The stream of nitrogen was then substituted by a stream of dry, purified acetylene and the operation was continued for 40 hours. The solution was poured into 100 cc. of dilute hydrochloric acid, the organic solvents were removed by steam distillation, the mixture was cooled and the precipitate was collected. Crystallization from chloroform - methanol yielded 2 - methyl - 17α - ethinyl-6-dehydro-estradiol.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3-propionate, 3-benzoate, 3-cyclopentylpropionate and the 3-phenylpropionate.

EXAMPLE IV

A solution of 0.5 g. of 2-methyl-6-dehydro - estrone in 25 cc. of ethyl acetate was stirred under an atmosphere of hydrogen, at room temperature and atmospheric pressure, in the presence of 100 mg. of a 10% palladium on charcoal catalyst. After the equivalent of one mol of hydrogen had been absorbed, the solution was filtered and evaporated to dryness. Crystallization from acetone-hexane yielded 2-methyl-estrone.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3-propionate, 3-benzoate, 3-cyclopentylpropionate and the 3-phenylpropionate.

0.3 g. of 2-methyl-estrone dissolved in 20 cc. of methanol was treated with a solution of sodium borohydride, as described in Example II, thus yielding 2-methyl-estradiol. This compound was 1/20 to 1/50 as estrogenic as estrone but had anti-androgenic activity.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3,17-dipropionate, 3,17-dibenzoate, 3,17-dicyclopentylpropionate and the 3,17-diphenylpropionate.

EXAMPLE V

The reaction of 2-methyl-estrone with potassium *t*-butylate and acetylene, in accordance with the conditions described in Example III, produced 2-methyl-17α-ethinyl-estradiol.

Conventional reaction of this compound with acid anhydrides and/or chlorides gave the corresponding 3-propionate, 3-benzoate, 3-cyclopentylpropionate and the 3-phenylpropionate.

WHAT WE CLAIM IS:—

1. In a process for the production of a 2 - methyl - 6 - dehydro-estrone compound, 2 - methyl - 6 - dehydro - estradiol compound, 2 - methyl - 17α - ethinyl-6-dehydro-estradiol compound, 2 - methyl - estrone compound, 2 - methyl - estradiol compound or 2 - methyl - 17α - ethinyl - estradiol compound, the step comprising heating 2 - methyl - $\Delta^{1,4,6}$ - androstatriene - 3,17 - dione to a temperature of approximately 600° C. to prepare 2 - methyl-6-dehydro-estrone.

2. The process of claim 1, wherein the heating is effected in the presence of mineral oil.

3. A process according to claim 1 substantially as herein described and exemplified.

4. The product obtained by the process claimed in any preceding claim.

5. 2 - Methyl - 6 - dehydro - estrone or an ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

6. 2 - Methyl - 6 - dehydro - estradiol or a diester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

7. 2 - Methyl - 17α-ethinyl - 6 - dehydro-estradiol or an ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

8. 2 - Methyl-estrone or an ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

9. 2-Methyl-estradiol or a diester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

10. 2-Methyl-17α-ethinyl-estradiol or an ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

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